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Clinical application value of Ultrafast Pulse Wave Velocity in early cardiovascular injury of Immunoglobulin A nephropathy

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Abstract

Aim: To investigate the application and the related influencing factors of ultrafast pulse wave velocity (ufPWV) in the evaluation of carotid artery elasticity in patients with Immunoglobulin A nephropathy (IgAN). **Material and methods:** A total of 156 IgAN patients and 50 healthy individuals were selected as the control group. The ufPWV technique was employed to measure carotid arterial elasticity parameters, including carotid intima-media thickness (cIMT), pulse wave velocity at the beginning of systole (BS-PWV) and pulse wave velocity at the end of systole (ES-PWV). **Results:** Across the three groups (control group, IgAN patients with normal renal function, and IgAN patients with renal dysfunction) there was an increasing trend observed in cIMT, BS-PWV, and ES-PWV. Additionally, ES-PWV exhibited higher sensitivity than BS-PWV. Correlation analysis revealed that BS-PWV and ES-PWV were positively correlated with age, body mass index (BMI), systolic blood pressure (SBP), high-sensitivity C-reactive protein (hs-CRP), creatinine (Cr), blood urea nitrogen (BUN), and uric acid (UA) and negatively correlated with estimated glomerular filtration rate (eGFR). **Conclusion:** The ufPWV technique allows for the rapid and direct measurement of arterial elasticity parameters in the neck and represents a novel approach for the early diagnosis and quantitative assessment of arterial stiffness risk in IgAN patients.

Keywords: ultrafast pulse wave velocity; carotid artery elasticity; immunoglobulin A nephropathy; estimated glomerular filtration rate

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide [1]. It typically exhibits a chronic progressive course, and approximately 10-20% of patients with IgAN progress to end stage renal disease within 20 years [2]. Research has shown [3] that the probability of cardiovascular disease occurrence in IgAN patients is 5 to 8 times higher than in the general population, with moderate to advanced cardiovascular damage being one of the primary causes of high mortality in IgAN patients. Metabolic abnormalities and changes in a state of low-grade inflammation are common pathological alterations in IgAN, closely associated with endothelial dysfunction [4]. These changes contribute to the development of atherosclerosis, leading to alterations in arterial elasticity. Therefore, early detection of changes in carotid artery elasticity in IgAN patients is beneficial in slowing down the progression of vascular damage and irreversible complications.

Pulse wave velocity (PWV) is considered the gold standard for assessing arterial elasticity and is recognized as one of the early predictors of cardiovascular events [5]. Ultrafast pulse wave velocity (ufPWV) is a rapidly evolving technique in recent years, allowing for the accurate measurement of carotid artery PWV and early assessment of arterial elasticity. Currently, ufPWV technology is mostly employed in studying changes in vascular elastic function in patients with metabolic diseases such

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as hyperlipidemia and hypertension, where structural changes in carotid arteries have already occurred [6,7].

There is limited research on vascular elastic function changes in IgAN patients with normal carotid artery morphology. In this study, ufPWV technology is utilized to quantitatively measure relevant parameters of carotid artery elasticity in IgAN patients, aiming to provide insights for clinical diagnosis and treatment.

Material and method

Patients

A total of 156 IgAN patients who sought medical care at Hangzhou Traditional Chinese Medicine Hospital from July 2019 to April 2022 were enrolled in this study. Among them, there were 74 males and 82 females, with ages ranging from 20 to 81 years, and an average age of (49.5±16.2) years. IgAN patients were divided into two groups based on their estimated glomerular filtration rate (eGFR) levels: the normal renal function group (eGFR≥90 mL/min) and the abnormal renal function group (eGFR<90 mL/min). This study primarily focused on patients with primary IgAN, and the exclusion criteria were as follows: severe cardiovascular diseases, including coronary heart disease, congestive heart failure, severe valvular regurgitation or stenosis, and severe peripheral arterial narrowing; severe liver diseases, malignant tumors, and patients with rheumatic diseases; patients with altered consciousness who could not cooperate with the examination; individuals with carotid artery plaque formation, tortuous carotid arteries, or poor image quality that could affect the analysis.

Additionally, 50 healthy volunteers from our hospital's health examination center during the same period were selected as the healthy control group. Among them, there were 22 males and 28 females, with ages ranging from 24 to 79 years and an average age of (54.1±15.2) years. All patients voluntarily participated in the study and provided informed consent. The study was approved by the hospital's Ethics Review Committee (Ethics Approval No. 2020KY119).

Methods

General information on all study subjects, including gender, age, height, body weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were collected. Additionally, laboratory data such as hemoglobin (Hb), fasting blood glucose (FBG), high-sensitivity C-reactive protein (hs-CRP), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), triglycerides (TG), eGFR, creatinine (Cr), uric acid (UA), and blood urea nitrogen (BUN) were gathered. Lastly, the ultrasound data, including carotid intima-media thickness (cIMT), brachial-ankle pulse wave velocity (BA-PWV), and carotid-femoral pulse wave velocity (CF-PWV) were obtained.

Instrumentation and operation

The Supersonic Imagine Aixplorer color Doppler ultrasound diagnostic system with technology was employed in this study, equipped with an SL10-2 probe with a frequency range of 2 to 10 MHz.

Patients were instructed to remain in a supine resting position with their head centered and slightly tilted upward. The clear and straight segment of the carotid artery was selected for measuring the carotid intima-media thickness (cIMT). Once the sampling box was designated, the system automatically tracked and outlined the intima and media layers with two dashed lines. The average IMT in that region was calculated. The sampling box width exceeded 1 cm, and this process was repeated three times, with the results recorded and averaged.

Subsequently, the above-mentioned area of interest was selected, and patients were instructed to hold their breath strictly for 5 seconds. After ensuring image stability, the system was switched to the ufPWV imaging mode. The system automatically traced and calculated the beginning of systole (BS) and ending of systole (ES) values for carotid artery PWV. Data with a $\Delta\pm\leq 1.0$m/s were considered qualified (fig 1). Measurements were repeated at least three times on the same carotid artery, and pulse wave velocity at the beginning of systole (BS-PWV) and pulse wave velocity at the end of systole (ES-PWV) values were separately recorded and averaged to obtain the final values. All ufPWV imaging examination images of the subjects were stored in the instrument and on the computer's hard drive.

Statistical analysis

Statistical analysis was conducted using SPSS 23.0 software. Continuous data were presented as mean±standard deviation(x±s), and independent sample t-tests were employed for comparison. Categorical data were analyzed using frequency composition ratios, and comparisons of rates were performed using the x±stest. A significance level of $p<0.05$ was considered statistically significant. Correlations among continuous data were assessed using Pearson or Spearman correlation analysis.

Results

General information

Statistical analysis revealed significant differences ($p<0.05$) between the IgAN group and the control group in various clinical parameters, including age, gender,

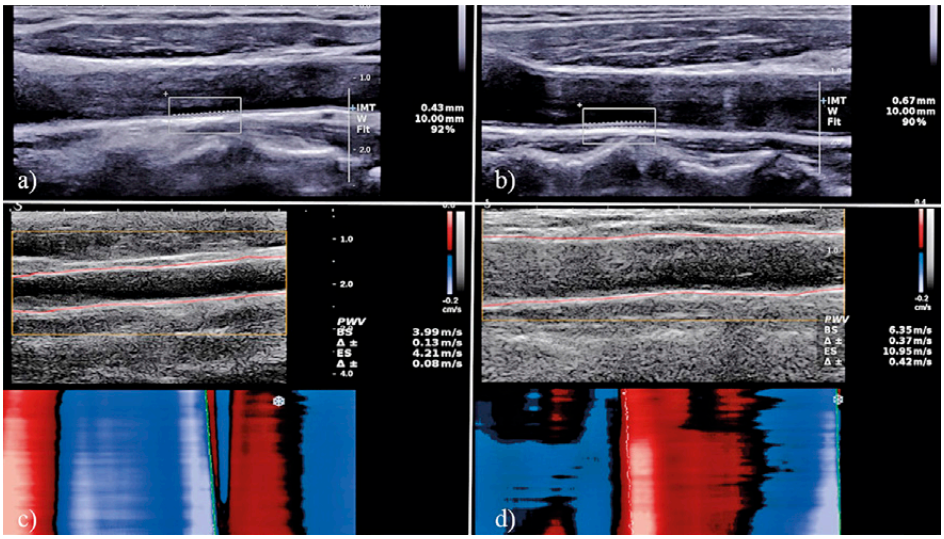

Fig 1. a) 2D ultrasound image: the average cIMT in the control group is 0.43 mm; b) 2D ultrasound image: the average cIMT in the IgAN group is 0.67 mm; c) Carotid artery ufPWV acquisition image: the carotid artery BS-PWV in the control group is 3.99 m/s, and ES-PWV is 4.21 m/s; d) Carotid artery ufPWV acquisition image: the carotid artery BS-PWV in the IgAN group is 6.35 m/s, and ES-PWV is 10.95 m/s. △±represents the standard deviation. Red indicates PWV motion toward the probe; blue represents PWV motion away from the probe; varying shades of color indicate relative PWV velocities.

body weight, Body Mass Index (BMI), smoking status, SBP, DBP, hs-CRP, Hb, LDL, Cr, BUN, UA, and eGFR. However, no statistically significant differences ($p>0.05$) were observed in clinical parameters such as height, FBG, TG, and HDL (Table I).

Comparison between groups of common carotid artery IMT, BS-PWV, ES-PWV

Statistically significant differences were observed (all $p<0.05$) in cIMT, BS-PWV, and ES-PWV when comparing the healthy control group to both the IgAN group with normal renal function and the IgAN Group with abnormal renal function. There was an increasing trend in the median values of cIMT, BS-PWV, and ES-PWV in both groups (Table II).

Pearson correlation analysis of patients with chronic kidney disease

In all the participants, BS-PWV showed a positive correlation with age, BMI, SBP, hs-CRP, Cr, BUN, and UA (all $p<0.05$), and a negative correlation with eGFR ($p<0.05$). However, it exhibited no significant correlation with body weight, height, DBP, Hb, FBG, TG, TC, LDL, or HDL (all $p>0.05$).

ES-PWV was positively correlated with age, BMI, SBP, hs-CRP, Cr, BUN, and UA (all $p<0.05$), and negatively correlated with Hb and eGFR ($p<0.05$). However, it showed no significant correlation with body weight, height, DBP, FBG, TG, TC, LDL, or HDL (all $p>0.05$) (Table III).

Discussion

Atherosclerosis forms the pathophysiological basis of cardiovascular diseases, and the decline in arterial elasticity is an early change, serving as an indicator for its early detection [8]. Hence, identifying reduced arterial elasticity at an early stage can aid in risk prediction, facilitating targeted prevention and treatment strategies. PWV is an independent predictor of cardiovascular disease risk and is considered a crucial indicator accurately reflecting arterial stiffness [9]. However, traditional PWV techniques have certain limitations [5]. They rely on measuring the time it takes for a pulse wave to travel between two pressure sensors, such as brachial-ankle or carotid-femoral, and estimating the distance between them. Traditional PWV can only reflect the average velocity between two vascular sites and may not accurately represent the true vascular stiffness at specific local lesions. Additionally, the human vascular system often has curved pathways, and the distance measurements between two arterial segments in traditional methods assume a linear path, leading to significant discrepancies between measured values and actual values. This affects PWV measurements and results in poor repeatability.

ufPWV is the latest non-invasive technique for assessing arterial elasticity [10]. With an image acquisition frequency of up to 10,000 frames per second, it precisely captures and measures the subtle movements and direction of arterial walls through rapid capture and calculation. This method extends the traditional two-point PWV

measurement to a single-probe distance, making it the only examination that can measure carotid artery PWV in a single acquisition. It allows for early evaluation of the degree of arterial stiffness before morphological changes occur in the blood vessels. The carotid artery, connecting two vital organs in the human body, the heart and the brain, shares a similar pathophysiological basis with coronary and cerebral artery atherosclerosis, making it a reflection of systemic arterial stiffness.

In this study, IgAN patients were divided into two groups based on their eGFR levels: the normal and abnormal renal function groups. The results revealed that patients in the abnormal renal function group had higher BS-PWV and ES-PWV compared to the normal renal function group (both $p<0.05$). Furthermore, as the renal function level decreased in IgAN patients, the degree of arterial stiffness gradually increased. These findings were consistent with previous studies on BA-PWV [11], which showed an increase in BA-PWV with decreasing eGFR. The analysis suggests that this may be due to impaired arterial elasticity, characterized by decreased expansiveness and increased stiffness, as a result of factors such as acid-base imbalance and electrolyte disturbances, which accompany the decline in eGFR. In the present study,

Table I. Comparison of general clinical data between the healthy control group and the IgAN group

Patients	Control group (n=50)	IgAN group (normal renal function) (n=67)	IgAN group (abnormal renal function) (n=89)	p-value
Age (year)	54.1±15.2	43.7±16.3	53.0±16.4	<0.001
Sex (%)				0.003
Man	43.1（22/51）	31.3（21/67）	58.4（52/89）	
Woman	56.9（29/51）	68.7（46/67）	41.6（37/89）	
Weight（kg）	59.3±9.1	63.2±13.6	64.4±10.9	0.042
Height（kg）	1.63±0.78	1.63±0.74	1.64±0.95	0.752
BMI (kg/m^2)	21.6±2.5	23.5±4.0	23.9±3.8	0.001
Current smoker	4	7	19	0.048
SBP (mmHg)	126.7±14.7	128.7±20.8	146.8±19.2	<0.001
DBP (mmHg)	78.7±9.4	76.5±14.1	85.1±13.9	<0.001
hs-CRP (mg/L）	1.4±2.2	2.3±2.0	5.0±3.0	<0.001
Hb (g/L)	128.0±15.8	123.2±15.9	109.8±25.5	<0.001
FBG (mmol/L)	4.91±0.74	5.03±1.44	5.18±2.33	0.683
TG (mmol/L)	1.41±1.50	1.63±1.17	1.73±1.23	0.347
TC (mmol/L)	4.57±1.10	5.35±1.74	4.99±1.64	0.043
LDL (mmol/L)	2.67±0.84	3.37±1.24	3.10±1.29	0.006
HDL (mmol/L)	1.09±0.24	1.16±0.35	1.16±0.42	0.421
Cr (μmol/L)	63.56±12.17	70.56±56.32	279.55±237.08	<0.001
BUN (μmol/L)	5.11±1.36	5.54±2.75	13.82±7.72	<0.001
UA (umol/L)	292.46±78.74	351.08±91.09	390.79±106.09	<0.001
eGFR	101.61±21.93	98.59±24.93	40．16±26.79	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; Cr, creatinine; UA, uric acid; BUN, blood urea nitrogen.

Table II. Comparison of carotid intima-media thickness (cIMT), pulse wave velocity at the beginning of systole (BS-PWV) and pulse wave velocity at the end of systole (ES-PWV) among the three groups (x±s)

Patients	cIMT (mm)	BS-PWV (m/s)	ES-PWV (m/s)
Control group	0.499±0.098	4.986±1.283	5.552±2.053
IgAN group (normal renal function)	0.554±0.144	5.531±1.833	6.753±2.062[a]
IgAN group (abnormal renal function)	0.677±0.210[ab]	6.223±2.295[a]	8.498±2.820[ab]
p-value	<0.001	<0.001	<0.001

Compared to the control group: [a]$p<0.001$; Compared to the IgAN (Normal Renal Function) group: [b]$p<0.001$; Compared to the IgAN (Impaired Renal Function) group: [c]$p<0.001$.

Table III. Pearson's correlation analysis between BS-PWV, ES-PWV and factors

	BS-PWV		ES-PWV	
	r	p	r	p
Age (year)	0.198	0.004**	0.316	0.000**
Weight（kg）	0.135	0.052	0.132	0.058
Height（cm）	0.007	0.923	0.023	0.737
BMI (kg/m^2)	0.175	0.012*	0.142	0.042*
SBP (mmHg)	0.197	0.005**	0.28	0.000**
DBP (mmHg)	0.055	0.433	0.083	0.233
hs-CRP (mg/L)	0.253	0.000**	0.298	0.000**
Hb (g/L)	-0.87	0.215	-0.168	0.016*
FBG (mmol/L)	0.115	0.099	0.12	0.086
TG (mmol/L)	0.129	0.065	0.095	0.174
TC (mmol/L)	0.123	0.078	0.069	0.323
LDL (mmol/L)	0.099	0.155	0.013	0.849
HDL (mmol/L)	0.071	0.307	0.125	0.074
Cr (μmol/L)	0.157	0.024*	0.317	0.000**
BUN (umol/L)	0.147	0.034*	0.377	0.000**
UA (umol/L)	0.237	0.001**	0.195	0.005**
eGFR	-0.277	0.000**	-0.433	0.000**

SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; Cr, creatinine; UA, uric acid; BUN, blood urea nitrogen. ** At the 0.01 level (two-tailed), the correlation is significant; * At the 0.05 level (two-tailed), the correlation is significant.

a negative correlation between eGFR and BS and ES values was observed, consistent with the research conducted by An et al [12]. The primary arterial changes in IgAN patients involve arterial dilation, followed by arterial wall thickening, and these alterations are closely associated with arterial elasticity.

This study assessed the influencing factors of BS-PWV and ES-PWV in IgAN patients and found positive correlations with age, BMI, SBP, hs-CRP, Cr, BUN, and UA. Among these factors, age was identified as an independent factor affecting ES-PWV. The rationale behind this observation is that with age, the vascular elastic tissue undergoes degenerative changes, with elastic tissue gradually being replaced by collagen tissue, ultimately leading to a decrease in arterial compliance [13]. The previous studies have shown that ufPWV measurements were an independent predictor of atherosclerosis in patients with hypertension and that ES-PWV could quantitatively evaluate arterial stiffness in healthy individuals [13,14]. Therefore, actively controlling blood pressure, improving renal function, and correcting vitamin D deficiency are crucial for improving arterial stiffness in IgAN patients.

In this study, UF-PWV technology was applied to measure IgAN patients and a healthy control group. The results showed that in the IgAN abnormal renal function group, cIMT, BS, and ES values were significantly higher compared to the healthy control group (all $p<0.05$). In the IgAN normal renal function group, the ES value was significantly higher than that of the healthy control group ($p<0.05$), while cIMT and BS in the normal renal function group showed no statistically significant differences compared to the healthy control group ($p>0.05$). Furthermore, when comparing the above parameters between the two IgAN patient groups, it was observed that BS and ES values in the IgAN abnormal renal function group were higher than those in the normal renal function group (both $p<0.05$). This suggests that in the presence of renal function abnormalities, vascular wall compliance begins to decrease, and arterial elasticity starts to decline even before significant changes in vascular structure occur. In other words, early structural changes indicative of arterial stiffness are already underway. Compared to BS values, ES values appear to be more sensitive to changes in vascular wall elasticity. On the other hand, in the IgAN normal renal function group compared to the healthy control group, cIMT did not show significant thickening. This indicates that as a traditional indicator of arterial stiffness, cIMT may not effectively capture differences in arterial stiffness changes between these two groups. It also suggests that changes in vascular elasticity occur earlier than changes in vascular structure, highlighting the potential use of PWV as an indicator for evaluating early-stage arterial stiffness.

In our study, arterial stiffness, as measured by ufPWV values, demonstrated an increase in carotid artery stiffness with advancing age. The ufPWV values indicated a strong correlation between age and arterial stiffness, consistent with previous ufPWV research. Furthermore, we found that, in comparison to BS-PWV, ES-PWV serves as a superior predictor of arterial stiffness, a finding in line with prior research [15]. This may be attributed to two related reasons: 1) from a technical perspective, regional ES-PWV offers a more accurate estimation than BS-PWV; 2) ES-PWV represents systolic arterial stiffness, making it more effective and sensitive in capturing changes in arterial stiffness induced by factors like age and related conditions.

This study has certain limitations. Firstly, the sample size was relatively small, and it is necessary to gather a larger number of samples in future research to validate the conclusions. Secondly, the study did not consider factors such as diurnal variations in vascular elasticity and the impact of subject fatigue on elasticity, which could introduce bias into the research data. Therefore, further

cross-sectional investigations are required to verify the aforementioned research findings.

Conclusion

In summary, ufPWV enables rapid and direct measurement of carotid artery elasticity parameters, allowing for the assessment of arterial stiffness in IgAN patients. This technology provides a new quantitative index and tool for the early and accurate evaluation of arterial elasticity in IgAN patients.

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Conflict of interest: none.

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